In the Specification:

Replace paragraphs 6, 8, 21, 22, 25, 32, 37, 42, 43, 172, 193, 194, 196, 197, 198, 200 and 202, and Tables 1, 2, 3, and 4, with the following rewritten paragraphs and tables.

[06] Polymorphisms in the human TIM-1 gene and exposure to Hepatitis A Virus (HAV) are shown to be associated with protection from the development of immunological disorders, such as atopy. A common polymorphism of TIM-1 in major human populations has an insertion at position 157, 157insMTTTVP SEQ ID NO:57. HAV seropositivity protects against atopy, but only in individuals with the 157insMTTTVP SEQ ID NO:57 allele. In some aspects of the invention the atopic disease is asthma. In other aspects, atopic disease is allergic rhinitis, and/or atopic dermatitis.

[08] In another embodiment of the invention, atopic individuals, particularly individuals having a TIM-1 genotype with at least one 157insMTTTVP SEQ ID NO:57 allele, are contacted with HAV or binding mimetics thereof, to diminish or terminate immunological disorders, such as atopy. In another embodiment of the invention, individuals having a TIM-1 genotype with at least one 157insMTTTVP SEQ ID NO:57 allele, are contacted with HAV or binding mimetics thereof to prevent the development atopy or other immunological diseases.

[021] Polymorphisms in the human TIM-1 gene and exposure to Hepatitis A Virus (HAV) are shown to be associated with protection from development of atopy. HAV seropositivity protects against atopy, but only in individuals with the 157insMTTTVP SEQ ID NO:57allele. TIM specific binding agents, including nucleic acids, antibodies, and the like, are useful as diagnostics for determining genetic susceptibility to atopy and asthma, including determination of the presence of the 157insMTTTVP SEQ ID NO:57 allele, which may be coupled with determination of HAV seropositivity status. The region of the TIM-1 polypeptide where the insertion is located is involved with viral uncoating; and may affect the extent and duration of HAV viremia. HAV interacts with monocytic cells and inhibits macrophage differentiation (see Wunschmann *et al.* (2002) *J Virol* **76**, 4350-6) and the HAV:TIM-1 interaction on progenitor cells may prevent the establishment, maturation, and maintainance of certain immune responses. The immune responses that may be regulated by TIM-1 include the T cell responses that underlie atopy and autoimmunity, and also include the immune responses that

determine susceptibility to various infectious diseases. HAV:TIM-1 binding may also directly impact the Th1/Th2 phenotype of TIM-1 expressing lymphocytes.

[022] In one embodiment of the invention, individuals, particularly individuals having a TIM-1 genotype with at least one 157insMTTTVP SEQ ID NO:57 allele, are contacted with HAV or binding mimetics thereof, to diminish or prevent pathological immune responses, such as those which occur in atopic diseases.

[025] Atopic diseases are complex conditions that develop as a result of environmentally induced immune responses in genetically predisposed individuals. Included among atopic conditions are asthma, allergic rhinitis (hay fever), atopic dermatitis (eczema) and food allergies. Both atopic and non-atopic individuals may be exposed to similar environmental factors, but genetic differences that distinguish atopic from non-atopic individuals result in atopic disease in some individuals, manifested by allergic inflammation in the respiratory tract, skin or gastrointestinal tract, as well as by elevated serum IgE, eosinophilia and the symptoms of wheezing, sneezing or hives. It is shown herein that exposure to HAV at levels sufficient to confer seropositivity confers protection from atopy in individuals that carry at least one TIM-1 157insMTTTVP SEQ ID NO:57 allele (SEQ ID NO:21 and 22). This allele is widely distributed in Asian, Caucasian, and African populations.

[032] Vaccination with inactivated or attenuated HAV can lead to seroconversion in a patient, and may protect against atopy in individuals carrying at least one 157insMTTTVP SEQ ID NO:57 allele. Inactivated hepatitis A vaccines have been developedand used in many countries. This virus is inactivated with formaldehyde and the antigen adsorbed to aluminum hydroxide and given intramuscularly. Attenuated strains of HAV have also been developed and may be useful potentially as vaccines. This approach may be advantageous because live vaccines tend to mimic the antibody response induced by natural infection. As with vaccine strains of polioviruses, attenuation may be associated with mutations in the 5' non-coding region of the genome which affect secondary structure. There is also evidence that mutations in the region of the genome encoding the non-structural polypeptides may be important for adaptation to cell culture and attenuation. While the biological basis for attenuation is unknown, three areas of the HAV genome may contain markers of attenuation. The RNAs of the 5' non-coding

regions of wild-type HAV and attenuated strains have different predicted secondary structures. The capsid region of the HAV genome may also be important for attenuation.

Please replace paragraph 37 on page 8 of the specification with the following paragraph:

[37] Polymorphisms in TIM sequences are provided in the sequence listing. In mouse TIM-1, these polymorphisms encode three amino acid differences and a fifteen amino acid deletion in HBA/DBA. Polymorphisms in coding regions of human *Tim1* include an insertion (labeled polymorphism 1, allele 3), 157insMTTTVP, ~~SEQ ID NO:38~~ SEQ ID NO:57, observed in 65% of the chromosomes, and a deletion (polymorphism 5), SEQ ID NO:39, 195ΔThr, observed in 65% of the chromosomes. Other polymorphisms are 157insMTTVP, T140A (polymorphism 7) SEQ ID NO:40; and single residue polymorphisms V161A; (polymorphism 2); V167I (polymorphism 3); T172A (polymorphism 4); N258D (polypmorphism 6). Polymorphism 4 was observed in 40% of the chromosomes, and the other polymorphisms were each observed in ≤5% of the chromosomes. Most of these variations (2-6) are located within exon 3, the first mucin-encoding exon, and all of the variants occur at the genomic level and are not splice variants.

Please replace paragraph 42 on page 10 of the specification with the following paragraph:

[042] In some embodiments, the Tim gene sequence is other than human TIM-1 allele 1, as set forth in the sequence listing. In one embodiment of the invention, the TIM-1 genetic sequence comprises an insertion encoding the amino acids MTTTVP (~~SEQ ID NO:21, residues 158-163~~ SEQ ID NO:57). In naturally occurring human genomes, this sequence is encoded by the genetic sequence, ATGACAACGACTGTTCCA, SEQ ID NO:22, bases 472-489. In combination with HAV seropositivity, this allele is protective for atopy, and therefore the presence of the allele is indicative that an individual may benefit from exposure to HAV for atopy treatment and/or prophylaxis. Determination of the presence of the allele may be determined by various methods known in the art, *e.g.* hybridization with a polynucleotide specific for the polymorphism.

Please replace paragraph 43 on page 11 of the specification with the following paragraph:

[43] The human 157insMTTTVP (SEQ ID NO:57) amino acid sequence is provided (SEQ ID NO:21), and the encoding gene as (SEQ ID NO:22). DNA encoding a 157insMTTTVP(SEQ ID

NO:57) amino acid sequence may be cDNA or genomic DNA or a fragment thereof that encompasses the inserted sequence, *e.g.* ATGACAACGACTGTTCCA, SEQ ID NO:22, bases 472-489. The term "ins157 gene", or "polymorphism 1" shall be intended to mean the open reading frame encoding such specific polypeptides, as well as adjacent 5' and 3' non-coding nucleotide sequences involved in the regulation of expression, up to about 1 kb beyond the coding region, in either direction.

[172] After sequencing *Tim1* from the chromosomes from 35 individuals (70 chromosomes) several polymorphisms in *Tim1* were identified, which are shown in Figure 8. These polymorphisms are numbered 1-7 (left column). The full sequence of human TIM-1, which is listed in the NCBI database (NM_012206), is provided in Figure 8 as a reference point. This sequence is present in less than 20% of the chromosomes that were sequenced, due to the existence of multiple, prevalent sequence polymorphisms in the coding region. 6 additional sequence variations were identified, shown in Figure 8, and all of the polymorphisms were observed in the mucin, extracellular domain, as was true for mice, although the specific variations were distinct from those seen in mice. Importantly, there is a limited degree of association between these variants, in various combinations. The most pronounced variations are the insertion labeled polymorphism 1, 157insMTTTVP SEQ ID NO:57, which was observed in 65% of the chromosomes, and the deletion in polymorphism 5, 187ΔThr, was observed in 65% of the chromosomes. Polymorphism 4 was observed in 40% of the chromosomes, and the other polymorphisms were each observed in ≤5% of the chromosomes. Notably, most of these variations (2-6) are located within exon 3, the first mucin-encoding exon, and all of the variants occur at the genomic level and are not splice variants.

[193] TIM-1 is expressed by activated CD4 T cells during the development of helper T cell (Th2) responses and appears to regulate cytokine production. Therefore, we postulated that HAV interaction with TIM-1 on lymphocytes could modify T cells in a manner that protects against atopy, and that polymorphisms in TIM-1 might alter susceptibility to atopy. By sequencing lymphocyte cDNA, we identified a six amino acid insertion, 157insMTTTVP SEQ ID NO:57. 157insMTTTVP SEQ ID NO:57 is located at the center of an extracellular mucin-like region that is required for efficient HAV uncoating, and because 157insMTTTVP SEQ ID NO:57 lengthens this critical region by 12-14%, this variation may impact the efficiency of viral entry.

[194] In order to determine whether 157insMTTTVP SEQ ID NO:57 contributes to atopy or to the protective effect of HAV, we examined the association between atopy and 157insMTTTVP SEQ ID NO:57 in a cross-sectional study of 375 individuals who were tested for serologic evidence of atopy and prior HAV infection. To correct for potentially confounding effects of population admixture, we used stratified Mantel-Haenszel chi-square tests to quantify the association between atopy and 157insMTTTVP SEQ ID NO:57 in the total sample. HAV seropositivity protects against atopy, but only in individuals with 157insMTTTVP SEQ ID NO:57 (P = 0.0005, Table 1). Thus, the protective effects of HAV depend upon a common TIM-1 allele, carried by 63% of Caucasians, 46% of Asians, and 64% of African Americans in this population.

[196] The mechanism underlying this interaction between TIM-1 and HAV may relate to the role of the 157insMTTTVP SEQ ID NO:57 region in viral uncoating, whether this polymorphism affects the extent and duration of HAV viremia, or whether HAV:TIM-1 binding directly impacts the Th1/Th2 phenotype of TIM-1 expressing lymphocytes.

Table 1: 157insMTTTVP TIM-1 alleles are associated with protection against atopy.

Study Subjects	Genotype	Number of Subjects with Atopic Disease			157insMTTTVP SEQ ID NO:57 *1,2 vs 0 alleles*		157insMTTTVP SEQ ID NO:57 *2 vs 0 alleles*		157insMTTTVP SEQ ID NO:57 *1 vs 0 alleles*	
		Total	Atopic N (%)	Nonatopic N (%)	χ^2 *P*	Odds Ratio (95% CI)	χ^2 *P*	Odds Ratio (95% CI)	χ^2 *P*	Odds Ratio (95% CI)
Total (n = 321)	Homozygous Insertion	48	28 (58)	20 (42)	*2.160*	0.703	*1.343*	0.668	*1.619*	0.721
	Heterozygous Insertion	137	86 (63)	51 (37)	**0.142**	(0.437-1.130)	**0.246**	(0.333-1.342)	**0.203**	(0.434-1.199)
	No Insertion	136	96 (71)	40 (29)						
HAV- (n = 198)	Homozygous Insertion	31	22 (71)	9 (29)	*0.463*	1.285	*0.860*	1.499	*0.389*	1.222
	Heterozygous Insertion	89	61 (69)	28 (31)	**0.496**	(0.708-2.439)	**0.354**	(0.614-3.663)	**0.533**	(0.644-2.320)
	No Insertion	78	50 (64)	28 (36)						
HAV+ (n = 123)	Homozygous Insertion	17	6 (35)	11 (65)	*11.978*	0.257	*9.879*	0.167	*8.242*	0.300
	Heterozygous Insertion	48	25 (52)	23 (48)	**0.0005**	(0.116-0.570)	**0.002**	(0.050-0.554)	**0.004**	(0.129-0.699)
	No Insertion	58	46 (79)	12 (21)						

[197] Table 1: Comparison of allele distributions across subjects using the Cochran-Mantel-Haenszel chi-square test (X^2) with racial stratification, two-sided tests of significance (P), and percent of (N) subjects with each genotype. Mantel-Haenszel common odds ratio estimates, presented in the supplemental data, demonstrate the lower likelihood of developing atopy with

157insMTTTVP SEQ ID NO:57 in the total sample of clearly atopic and clearly nonatopic subjects, consisting of Caucasians (n = 210), Asians (n = 100), and African Americans (n = 11). As an independent variable, 157insMTTTVP SEQ ID NO:57 is not associated with atopy (÷ 2 = 2.160, P = 0.142), while 157insMTTTVP SEQ ID NO:57 in HAV+ individuals (÷ 2 = 11.98, P = 0.0005) is associated with atopy, and HAV does not independently affect atopy (X^2 = 0.513, P = 0.474, respectively). Importantly, allelic variation in TIM-1 does not affect HAV infection rates in our population (X^2 = 1.567, P = 0.211), therefore, the TIM-1:HAV genetic interaction in this study is not attributable to different rates of seroconversion following HAV exposure. Subgroup analyses of Caucasians and Asians confirm this association in both groups (P = 0.024 and P = 0.036, respectively), and Breslow-Day tests of the homogeneity of the odds ratios demonstrate no significant differences between the racial strata (supplemental data, Tables S3 and S4), although the frequency of the insertion allele is somewhat greater in Caucasians (0.39) than in Asians (0.26). The African American sample size was too small to present separately.

Table S2: HAV exposure reduces the risk of atopy in individuals with 157insMTTTVP alleles.

157insMTTTVP SEQ ID NO:57 Allele Copy Number	HAV Exposure	Number of Subjects with Atopic Disease		Allele:HAV Interaction χ^2	Allele:HAV Interaction *P (two-sided)*	Allele:HAV Interaction Odds Ratio (95% CI)
		Atopic	Nonatopic			
0 (*n* = 136)	HAV-	50	28	2.817	**0.093**	1.937 (0.882-4.253)
	HAV+	46	12			
1 (*n* = 137)	HAV-	61	28	3.536	**0.060**	0.503 (0.243-1.041)
	HAV+	25	23			
2 (*n* = 48)	HAV-	22	9	5.373	**0.020**	0.251 (0.074-0.858)
	HAV+	6	11			
1, 2 (*n* = 185)	HAV-	83	37	8.289	**0.004**	0.411 (0.221-0.764)
	HAV+	31	34			

[198] Table 2. Influence of HAV exposure on 157insMTTTVP SEQ ID NO:57 allele specific protection against atopy. Cochran-Matel-Haenszel chi-square statistics and Mantel-Haenszel common odds ratio estimates for atopy in subjects with each genotype, with or without prior HAV exposure demonstrate a significant interaction between 157insMTTTVP SEQ ID NO:57 genotypes and HAV exposure. Individuals who carry at least one 157insMTTTVP SEQ ID NO:57 allele are protected from atopy in a manner that depends upon HAV exposure. Although these data are suggestive of susceptibility in seropositive individuals without 157insMTTTVP SEQ ID NO:57 (OR = 1.94), this finding is not significant (CI, 0.882 - 4.255). An apparent dosage effect is observed, such that individuals with two copies of the 157insMTTTVP

SEQ ID NO:57 allele are afforded more protection from atopy (OR = 0.251; CI, 0.074 - 0.858) than individuals who carry only one (OR = 0.503; CI, 0.243 - 1.041).

Table S3: 157insMTTTVP TIM-1 alleles protect against atopy in Caucasians.

Caucasian Subjects	157insMTTTVP SEQ ID NO:57 Allele Copy Number	Number of Subjects with Atopic Disease			157insMTTTVP SEQ ID NO:57 *1,2 vs 0 alleles*		157insMTTTVP SEQ ID NO:57 *2 vs 0 alleles*		157insMTTTVP SEQ ID NO:57 *1 vs 0 allele*	
		Total	Atopic N (%)	Nonatopic N (%)	χ^2 *P*	Odds Ratio (95% CI)	χ^2 *P*	Odds Ratio (95% CI)	χ^2 *P*	Odds Ratio (95% CI)
Total ($n = 210$)	2	36	20 (56)	16 (44)	*0.340*	0.841	*1.013*	0.662	*0.064*	0.922
	1	96	61 (64)	35 (36)	0.560	(0.469-1.506)	0.314	(0.296-1.481)	0.801	(0.494-1.724)
	0	78	51 (65)	27 (35)						
HAV- ($n = 142$)	2	23	15 (65)	8 (35)	*0.781*	1.379	*0.132*	1.209	*0.896*	1.443
	1	68	47 (69)	21 (31)	0.377	(0.676-2.817)	0.716	(0.434-3.378)	0.344	(0.674-3.096)
	0	51	31 (61)	20 (39)						
HAV+ ($n = 68$)	2	13	5 (38)	8 (62)	*5.119*	0.302	*4.748*	0.219	*3.375*	0.350
	1	28	14 (50)	14 (50)	**0.024**	(0.105-0.870)	0.029	(0.053-0.896)	0.066	(0.112-1.089)
	0	27	20 (74)	7 (26)						

Table S4: 157insMTTTVP TIM-1 alleles protect against atopy in Asians.

Asian Subjects	157insMTTTV SEQ ID NO:57 P Allele Copy Number	Number of Subjects with Atopic Disease			157insMTTTVP SEQ ID NO:57 *1,2 vs 0 alleles*		157insMTTTVP SEQ ID NO:57 *2 vs 0 alleles*		157insMTTTVP SEQ ID NO:57 *1 vs 0 allele*	
		Total (%)	Atopic N (%)	Nonatopic N	χ^2 *P*(Fisher)	Odds Ratio (95% CI)	χ^2 *P*(Fisher)	Odds Ratio (95% CI)	χ^2 *P*(Fisher)	Odds Ratio (95% CI)
Total ($n = 100$)	2	7	4 (57)	3 (43)	*4.246*	0.398	*1.772*	0.341	*3.680*	0.409
	1	39	24 (62)	15 (38)	0.039	(0.164-0.967)	0.335	(0.066-1.754)	0.065	(0.162-1.032)
	0	54	43 (80)	11 (20)						
HAV- ($n = 49$)	2	4	3 (75)	1 (25)	*0.523*	0.632	*0.002*	0.947	*0.654*	0.586
	1	20	13 (65)	7 (35)	0.538	(0.181-2.203)	1.000	(0.082-10.870)	0.515	(0.160-2.150)
	0	25	19 (76)	6 (24)						
HAV+ ($n = 51$)	2	3	1 (33)	2 (67)	*4.796*	0.250	*3.886*	0.104	*3.594*	0.286
	1	19	11 (58)	8 (42)	**0.036**	(0.070-0.897)	**0.113**	(0.008-1.383)	0.096	(0.076-1.079)
	0	29	24 (83)	5 (17)						

[200] Possible mechanisms include an effect wherein 157insMTTTVP alters an effect of HAV on TIM-1 expressing T cells during Th2 activation and differentiation. Alternatively, 157insMTTTVP SEQ ID NO:57 may alter the virus-receptor interaction at the mucin domain of TIM-1 and thereby enhance HAV viral uncoating and infection.

[202] *Identification of Polymorphisms:* Peripheral blood mononuclear cells (PBMC) were obtained from 23 of these subjects, purified according to standard protocols and polyclonally activated with ConA or with PHA and PMA in vitro, prior to purification and reverse transcription of total RNA. The complete coding region of TIM-1 was amplified and sequenced with dye terminating methods at the Stanford Protein and Nucleic Acid facility, using the following primers for PCR with Herculase Hot Start Polymerase (Stratagene), (SEQ ID NO:37) 5'-GGAATTCGTCGACCACCATGCATCCTCAAGTGGTCATCTTA-3' and (SEQ ID NO:38) 5'-GGAATTCGCGGCCGCTCATTAGTCCGTGGCATAAACAGTATT-3', and for sequencing, (SEQ ID NO:39) 5'- TCAAGTGGTCATCTTAAGCC-3', (SEQ ID NO:40) 5'-TAAACTCTCAAAG-AGCACCACT-3', (SEQ ID NO:41) 5'-ACAGACTCCAGCATAGATTCCT-3', (SEQ ID NO:42) 5'-GCACCAA GACAGAAATACAGAC-3', and (SEQ ID NO:43) 5'-AGAAGCACCCAAGACAGAAATACAGACTCCA-3'. The following nonsynonymous changes were identified by comparing our sequences to the NCBI reference sequence AF043724: 157insMTTTVP SEQ ID NO:57, 195delT, and A206T. To validate these polymorphisms, TIM-1 cDNA from five heterozygous donors was cloned into TOPO-TA sequencing vectors (Invitrogen) and sequenced. Genomic sequence was examined to confirm that the polymorphisms described are attributable to genomic polymorphisms within exons, not alternate splicing.